REMARKS

Claims 49-52, 56-60, 64 and 68-83 are pending and under examination. Claims 49 and 57 have been amended. Support for the amendments can be found throughout the application as filed including, for example, at page 4, paragraph 2, lines 4-5. Accordingly, no new matter has been introduced and entry thereof is respectfully requested.

Information Disclosure Statement

Consideration of the Information Disclosure Statements filed June 18, 2009, and July 9, 2009, is acknowledged. However, the Examiner contends that the citations stricken through on the Information Disclosure Statement of June 18, 2009, have not been provided.

Applicant respectfully points out that copies of the references corresponding to the stricken citations marked with two asterisks on the June 18, 2009, Information Disclosure Statement were provided in the Statement filed July 9, 2009. Each citation marked with two asterisks was footnoted with the notation that the indicated reference "[w]ill be provided under separate cover." Copies of those references were filed on July 9, 2009. For the Examiner's convenience, replacement copies of these references and a clean copy of the Communication as it was filed on July 9, 2009, is attached as Exhibit 1. Applicant respectfully requests that these references be considered and made of record.

With respect to the citations stricken by the Examiner marked with three asterisks. These publications correspond to URLs that were unavailable as of Applicant's submission. Applicant submits herewith a Supplemental Information Disclosure Statement providing the complete citation for these URL publications and attaching a copy of the relevant page of each publication. Citations 369, 371, 376 and 383 were pointed out by the Examiner to be missing dates. As stated above, these citations have been corrected. Applicant notes that the Examiner has requested a complete copy of the entire database. This request appears unreasonable in light of the Office's current practice of providing only the pertinent page(s) for electronic databases. If there are particular pages the Examiner does not have access to and would like to review Applicant would be glad to supply those pages. Accordingly, Applicant respectfully requests that these references be considered and made of record.

Applicant has also addressed in the attached Supplemental Information Disclosure Statement particularities raised by the Examiner in the Office Action. In this regard, reference #285, Schilling (2000), is relisted and a complete copy of this publication has been provided. Similarly, the citations to 6,500,710 (Thalhammer-Reyero) and 6,902,692 (Palsson et al.) have been relisted (Thalhamme-Reyero) or omitted (Palsson) to correct the typographical errors. Applicants respectfully request that this reference be made of record.

Rejections Under 35 U.S.C. § 103

Claims 49-52, 56-60 and 68-83 stand rejected under 35 U.S.C. § 103(a) for allegedly being obvious over over Pramanik et al., *Biotechnol. Bioengineer.* 56:396-421 (1997), in view of Blattner et al., *Science* 277:1453-1469 (1997) and in view of Kunst et al., *Rev. in Microbiol.* 142:905-12 (1991). Pramanik et al. is cited for allegedly describing a stoichiometric model of *E. coli* metabolism. Blattner et al. allegedly describe mapping the *E. coli* genome and assigning function to proteins by determining similarity to proteins of known function. Kunst et al. is cited for allegedly identifying sequences of unknown function and assigning function to these sequence by homology comparison to sequences of known function. The Examiner stepwise rebuts some of Applicant's arguments filed in the previous response. Applicant will address each rebuttal in turn below.

Conclusory Reliance on Kunst et al. Fails to Address the Claims

In concluding that Applicant's arguments with respect to the cited art are unpersuasive the Examiner appears to pick and choose what statements to address without consideration of context or consideration for the entirety of the argument. The Examiner points out that Applicant first argues that Pramanik et al. teach only known genes encoding proteins with known biological activity and concludes that the remarks are unpersuasive with respect to overcoming the rejection because Kunst et al. is cited for this rationale. Applicant presumes that the Examiner means that Kunst et al. is cited allegedly for identifying and assigning function to sequences of unknown function by homology comparison with sequences in other organisms. This limited conclusion fails to address Applicant's remarks with respect with respect to the secondary references of Blattner et al. and Kunst et al.; the combination of reference as a whole; the general knowledge in the art, nor with respect to the requirements that must be satisfied

under *KSR v. Teleflex, Inc, et al.*, 127 S. Ct. 1727 (2007) in order to establish a *prima facie* case of obviousness.

With respect to Applicant's remarks related to Pramanik et al., Applicant merely acknowledge that already conceded by the Office. Namely, that Pramanik et al. lists known genes encoding proteins of known function. However, Applicant also pointed out that, based on the statements made by Pramanik et al., one would conclude that there is no benefit to include metabolic reactions deduced from open reading frames of genes of unknown function. The Examiner failed to address this rationale for rebutting the cited combination of references.

With respect to Blattner et al., Applicant also pointed out that which was conceded by the Office, namely, that Blattner et al. reports on the sequencing of the *E. coli* genome. Previous arguments of record pointed out that because Blattner et al. teach that more than one third of the open reading frames (ORFs) in the *E. coli* genome could not be attributed a function and that close to two thirds have no match in another organism, the combination of Blattner et al. with Pramanik et al. would not lead one of ordinary skill in the art to construct an *in silico* model as claimed. This argument appeared persuasive because this ground of rejection was withdrawn and the current rejection issued which additionally applied Kunst et al. However, as set forth in Applicant's previous response and again below, Kunst et al. is redundant with Blattner et al. and provides little, if anything, new to the previously withdrawn rejection because both Blattner et al. and Kunst et al. analyze their respective genomes by homology sequence comparisons.

In this regard, the further combination with Kunst et al. fails to improve on this combination of references because Blattner et al. did do sequence comparisons and found that, despite such comparisons, a large fraction of the *E. coli* ORFs could not be assigned a function based on homology and that a significant majority of the polypeptides encoded by the *E. coli* ORFs had no match in another organism. As described below and previously of record, Kunst et al. similarly admits that the majority of genes will have unknown function after sequence analysis.

Hence, Blattner et al. and Kunst et al. are duplicative and neither would lead one to arrive at the claimed invention when combined with Pramanik et al. because there is insufficient specificity in identifying an encoded protein and accurately assigning a function when it is

deduced from genomic sequence information. Applicant has amended the claims to more explicitly recite that the functions of the metabolic genes in the claimed invention are potential functions assigned by the claimed comparisons. Based on the cited art, one skilled in the art would not have assigned potential functions to proteins encoded by open reading frames of unknown function by determining homology to genes of known function and incorporated such potential reactions unconfirmed by experimental evidence into an *in silico* reconstruction because some of the reactions would have incorrect assignments as metabolic genes that would lead to aberrant fluxes. The declarations of record by Drs. Keasling, Palsson and Nielson attest to this conclusion.

As Applicant has set forth above and previously of record, Kunst et al. fails to improve on the deficiencies in the earlier combination of Pramanik et al. with Blattner et al. and would not have led one of ordinary skill in the art to arrive at the claimed invention when combined with Blattner et al. and Pramanik et al. The Examiner still appears not to have addressed this argument.

With respect to Kunst et al., the Examiner newly applied this reference because "the 'unknown' functions of protein sequences are identifiable by homology comparison with corresponding sequences in other organisms." Office Action mailed Dec. 18, 2008, page 8, para. 1 (quotes original). However, the support cited by the Examiner is the passage in Kunst et al. that expressly teaches that the majority of genes will not have either (1) a known function or (2) sequence similarity with proteins in other organisms. Therefore, the function of these genes will be unknown. Kunst et al., page 905, para. bridging columns 1 and 2.

As Applicant points out above, there is no reason provided why one of ordinary skill in the art would arrive at the claimed invention in light of a large number of genes that have no identifiable function or match in another organism. Nor would such a large number of genes with unidentifiable function motivate one to incorporate such information into a model of the invention. Applicant pointed these deficiencies out in the Response filed June 18, 2009, when Applicant stated:

> A teaching that a majority of genes will have an unknown function fails to provide any incentive or motivation for one to combine Pramanik et al. and

> Blattner et al. with Kunst et al. because it informs the skilled person in the art that there is a high likelihood that incorrect information will be incorporated into the model. Incorrect assignment and incorporation into a stoichiometric model of putative metabolic genes or genes with unknown function as a metabolic gene will lead to inaccurate fluxes and diminution in the ability of the model to correctly simulate or predict a phenotype of the microbial organism. Accordingly, both Blattner et al. and Kunst et al., while they report on sequenced genomes and comparative analysis, teach that one skilled in the art, upon a careful reading of Pramanik et al., Blattner et al. and Kunst et al., would not be motivated to combine these references to arrive at the invention as claimed because incorporation of incorrect information leading to a less predictive model is a likely possibility.

Id., page 10, para. 2 (emphasis added).

The Examiner's comments with respect to the above point was that these arguments were not persuasive because: (1) the comparison of homologies results from the combination of Kunst et al., Pramanik et al. and Blattner et al., and (2) there would have been a reasonable expectation of success in combining the stoichiometric matrices corresponding to known biological functions in Pramanik et al. and Blattner et al. with the sequences of Kunst et al. having unknown function because the functions and structural stoichiometries of the relations in Pramanik et al. are analogous to the kinetics of homologous organisms as taught in Kunst et al.

Applicant respectfully submits that the first point appears to be nothing more than a conclusion and fails to address Applicant's rebuttal. Additionally, the comparison of homologies might result from the cited combination, but such a comparison fails to lead one of ordinary skill to arrive at the invention as claimed.

The invention claims assigning a potential function to most metabolic genes. Both Blattner et al. and Kunst et al. each teach that a large number of the genes analyzed by sequence comparison will not have an identifiable function or a sequence similarity in another organism. Accordingly, the cited combination fails to teach, suggest or provide any incentive for one of ordinary skill in the art to arrive at the claimed invention because the art teaches that the putative functions of most metabolic genes cannot be obtained since the majority will have no homology match in another organism. Similarly, common general knowledge could not lead one of ordinary skill in the art to arrive at the claimed invention in light of the cited art because the

common general knowledge is that putative functions cannot be assigned for most metabolic genes since a majority of the genes will have not have a homology match in another organism.

With respect to the second point, Applicant fails to see the relevance or rationale for this statement. The functions of the relations, structural stoichiometries of the relations and kinetics of homologous organisms as stated in the Office Action does not appear to be relevant to the invention as claimed. In particular, what relations, structural stoichiometries and relations and kinetics of homologous organisms is being referred to in the Office Action? Applicant respectfully requests that should the Examiner maintain this rationale that the reasoning be explained with particularity as it applies to the claimed invention and the nonobvious arguments set forth above and previously of record.

With respect to the additional point that the motivation to combine exists because use of the entire genome provides for further analysis of metabolism and permits new ways at looking at the evolutionary history. Applicant respectfully maintains that such an alleged motivation fails to address the claimed invention because it fails to provide a teaching or incentive for curing that which is deficient in the cited combination. Blattner et al. and Kunst et al. each teach that a majority of genes, including metabolic genes, do not have a homology match in another organism. Therefore, one of ordinary skill in the art will conclude from Blattner et al. and Kunst et al. is that there will be metabolic genes that will not have a homology match and that it would not be likely to accurately assign a potential function to these genes. The rationale that the entire genome provides for further analysis and permits new ways of looking at evolutionary history fails to address the gap acknowledged by both Blattner et al. and Kunst et al. that the majority of genes will not have a homology comparison. Without such homology information for the genes that do not have matches in another organism the cited combination cannot render obvious claimed invention absent hindsight analysis by the Office.

With respect to the satisfaction of all requirements under *KSR*, Applicant additionally pointed out above and previously in the Response filed June 18, 2009, that the genome sequence described by Blattner et al. or the homology comparisons described by Kunst et al. also fail to provide any general knowledge that would contain an incentive to motivate one skilled in the art to incorporate the genomic information into an *in silico* reconstruction because a sizeable

fraction of the genes cannot be assigned a function or exhibit a homology match in another organism. Similarly, there has been no explanation that Applicant is aware of where the Examiner has included an explanation of "the effects of demands known to the design community or present in the marketplace" and "the background knowledge possessed by a person having ordinary skill in the art." *KSR Int'l. Co. v. Teleflex, Inc., et al.*, 127 S. Ct. 1727 (2007). It is respectfully submitted that the Office falls short of providing the requisite analysis.

Declarations by Drs. Keasling, Palsson and Nielsen Show Lack of Motivation and Unexpected Results of Claimed Invention Over the Cited Art

With respect to the Nielsen declaration stated to not have been received, Applicant submits as Exhibit 2 the Response and related papers download from PAIR of the filing on June 18, 2009, together with the electronic filing receipt. The electronic filing receipt shows that a 176 page Response was filed. The Nielsen declaration begins on page 137 of the Response, which corresponds to page 145 of complete filing attached as Exhibit 2. The declarations appear as a separate document in PAIR, where the Nielsen declaration can be found at page 92 of the 131 page document entitled "06-18-2009 Rule 130, 131 or 132 Affidavits." Applicant respectfully requests that the Examiner consider this declaration for the record.

With respect to the declaration submitted by Dr. Keasling, the Examiner concludes that the unexpected results set forth therein are not persuasive because Kunst et al. teache that structures and functions of sequences with unknown function can be determined by comparison. The Examiner further concludes that Kunst et al. describe that such comparisons result in improvement in expression of industrially important enzymes.

Applicant respectfully points out that the above rationale fails to address that the majority of genes do not have an homology comparison and that, based on the cited art, one would not have expected incorporations of genes having potential functions to result in a model that was predictive. As set forth above and previously of record, absent a homology comparison for most genes one of ordinary skill in the art could not have had a reasonable expectation of success of incorporating most putative metabolic genes and obtaining a predictive model. Further, identification of some putative metabolic genes was speculative and expected to result in incorporation of inaccurate reactions. Dr. Keasling's declaration attests to these points as well as

to the unexpected results obtained by incorporation of potential metabolic genes identified by sequence comparison. If Dr. Keasling, as the senior author on the primary cited reference, did not consider incorporation of genomic information based on, for example, the publication by Blattner et al. then it is very unlikely that one of ordinary skill in the art would have considered it as well.

With respect to the declaration submitted by Dr. Palsson, the Examiner again appears to summarily conclude that the motivation and reasonable expectation of success is provided because the cited art provides for homology comparisons and because the functions and structural stoichiometries of the relations are analogous to the kinetics of homologous organisms. The Examiner further concludes that Dr. Palsson's declaration was directed to the secondary consideration of long felt need and fails to accord it due weight apparently because no direct evidence in the scientific or patent literature was supplied.

As pointed out above, the cited combination does not lead one of ordinary skill in the art to arrive at the claimed invention because a majority of genes in both Blattner et al. and Kunst et al. do not have a sequence match in another organism. Therefore, based on the cited art one would not have an incentive or reasonable expectation of success of identifying most potential metabolic genes, incorporating that information into a model as claimed and arriving at a model that is predictive of an microbe's phenotype. Dr. Palsson's declaration attests to this point.

With respect to the second point, Applicant does not see the relevance of the rationale regarding relations and kinetics as applied to the claimed invention and respectfully requests that, should the Examiner maintain this reasoning, that he explain with particularity how it applies to the claimed invention.

With respect to the characterization of Dr. Palsson's declaration, Applicant respectfully points out that Dr. Palsson attests that there was a lack of motivation and reasonable expectation of success to incorporate genomic data or sequence comparisons because the model's predictability would have been expected to be reduced. The declaration does not intend to offer evidence of a long felt need nor is there a requirement for direct evidence in the literature. The letter by Dr. Bailey, a well known leader in the field, nevertheless provides direct evidence sufficient for showing a lack of motivation and a reasonable expectation of success. Dr. Bailey's

letter states that Dr. Palsson's model was not expected to work (showing a lack of a reasonable expectation of success) and if it did work, that such a result was a breakthrough (showing an unexpected result). Applicant contends that this evidence should be given ample weight for a showing of nonobviousness over the cited art.

In light of the above remarks, Applicant contends that the invention as claimed in unobvious over the cited art and respectfully requests withdrawal of this ground of rejection.

Claim 64 stands rejected under 35 U.S.C. § 103(a) as allegedly obvious over Pramanik et al. in view of Blattner et al., in view of Kunst et al. and further in view of Xie et al., *TIBECH* 15:109-113 (1997). Pramanik et al., Blattner et al. and Kunst et al. are applied as described above. Xie et al. allegedly describes integrated approaches to the design of media and that the composition of growth medium and its depletion over time affects growth of cells. The Examiner alleges that it would have been obvious to one of ordinary skill in the art to modify the studies of *E. coli* of Pramanik et al., Blattner et al. and Kunst et al. by the nutrient depletion studies of Xie et al. because stronger media can be designed to enable better growth of cells.

The rejection of claim 64 relies on the primary reference by Pramanik et al. in combination with Blattner et al. and Kunst et al. The deficiencies of this combination are detailed above and in the previously submitted Declarations by Drs. Keasling, Palsson and Nielsen. The tertiary reference to Xie et al. does not address, much less cure these deficiencies, which are fatal to the instant obviousness rejection. Accordingly, Applicants respectfully request withdrawal of the rejection of claim 64 under 35 U.S.C. § 103 as obvious over Pramanik et al. in view of Blattner et al. and Kunst et al. as applied to claims 49-52, 56-60 and 68-83, and further in view of Xie et al.

Provisional Double Patenting

Claims 49-52, 56-60 and 64 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly obvious over claims 26-28, 30, 32, 35, 36, and 39-41 of copending application serial No. 11/980,199.

Applicant respectfully requests deferral of this provisional ground of rejection until such time that there is an indication of allowable subject matter. Per Applicant's previous response,

should the subject application be deemed in conditions of allowance prior to application serial No. 11/980,199, Applicant respectfully requests that this provisional rejection be withdrawn in this earlier filed application and permit it to proceed to issuance without need of a terminal disclaimer. MPEP § 804(I)(B).

CONCLUSION

In light of the amendments and remarks herein, Applicant submits that the claims are now in condition for allowance and respectfully requests a notice to this effect. The Examiner is invited to call the undersigned if there are any questions.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

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